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Evidence of pleiotropic effects on the heart and other organs:
An expert panel position paper

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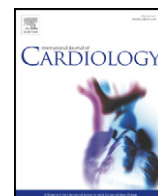
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Review

Levosimendan beyond inotropy and acute heart failure: Evidence of pleiotropic effects on the heart and other organs: An expert panel position paper



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ABSTRACT

Levosimendan is a positive inotrope with vasodilating properties (inodilator) indicated for decompensated heart failure (HF) patients with low cardiac output. Accumulated evidence supports several pleiotropic effects of levosimendan beyond inotropy, the heart and decompensated HF. Those effects are not readily explained by cardiac function enhancement and seem to be related to additional properties of the drug such as anti-inflammatory, anti-oxidative and anti-apoptotic ones. Mechanistic and proof-of-concept studies are still required to clarify the underlying mechanisms involved, while properly designed clinical trials are warranted to translate preclinical or early-phase clinical data into more robust clinical evidence. The present position paper, derived by a panel of 35 experts in the field of cardiology, cardiac anesthesiology, intensive care medicine, cardiac physiology, and cardiovascular pharmacology from 22 European countries, compiles the existing evidence on the pleiotropic effects of levosimendan, identifies potential novel areas of clinical application and defines the corresponding gaps in evidence and the required research efforts to address those gaps.

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1. Introduction

Levosimendan is a positive inotropic agent with vasodilating properties, also termed inodilator [1,2]. It acts on one hand by increasing the sensitivity of troponin C to calcium in myocardial cells, hence leading to inotropy, and on the other by opening the mitochondrial adenosine triphosphate (ATP)-sensitive potassium channels in smooth muscle cells, thus resulting in vasodilatation (Fig. 1). At higher doses, the drug also acts as a phosphodiesterase III inhibitor [1]. In addition, it also activates ATP-sensitive potassium channels in mitochondria, an effect that seems to hold a key role in protecting myocardial and potentially other cell types against ischemia/reperfusion injury and perhaps other insults. Levosimendan is currently indicated as an inotrope for acutely decompensated heart failure patients with low cardiac output.

There is an accumulated body of preclinical and clinical evidence indicating that levosimendan may be beneficial for organs besides the heart and in conditions beyond acute heart failure. In addition to the expected improvement of peripheral organs by virtue of the enhancement of cardiac function, those beneficial effects seem to be related to additional or pleiotropic properties of the drug beyond inotropy. As a result, favorable effects have been documented in cardiac and non-cardiac conditions other than acute heart failure.

The scope of the present position paper is to compile the evidence on the pleiotropic effects of levosimendan and its potential use besides the established indication. More specifically, the paper assembles the existing pieces of evidence on the pleiotropic effects of levosimendan, identifies potential novel areas of clinical application and defines the corresponding gaps in evidence and thus the required research efforts

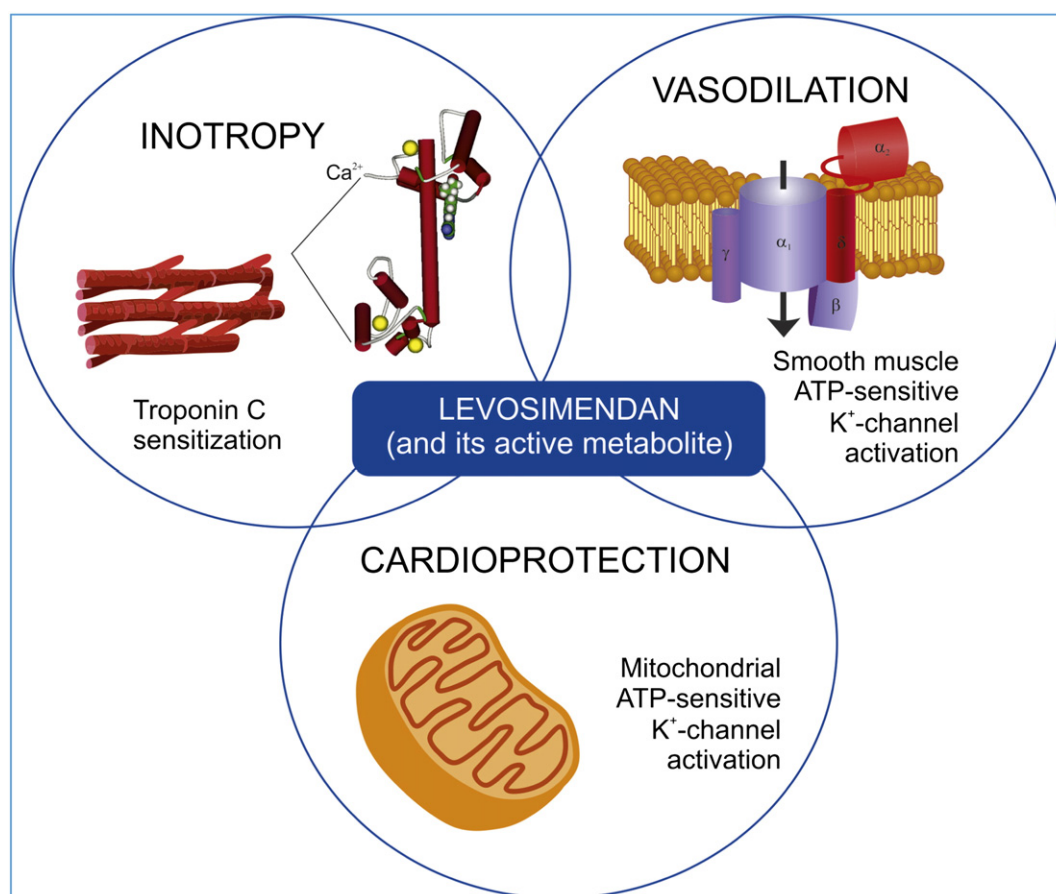


Fig. 1. Levosimendan's main mechanisms of action (modified from Papp Z et al. Int J Cardiol 2012;159:82–7).

to address those gaps. It was derived by a panel of 35 experts in the field of cardiology, cardiac anesthesiology, intensive care medicine, cardiac physiology, and cardiovascular pharmacology from 22 European countries (Austria, Belgium, Croatia, Czech Republic, Denmark, Finland, France, Germany, Greece, Hungary, Israel, Italy, Poland, Portugal, Russia, Slovenia, Spain, Sweden, the Netherlands, Turkey, the United Kingdom, and Ukraine) with an expertise on levosimendan, who convened in Athens on February 26–27, 2016 for reviewing the existing data on the pleiotropic effects of levosimendan on the heart and non-cardiac organs.

2. Levosimendan beyond inotropy: pleiotropic effects on the cardiovascular system

2.1. Relaxation and diastole

Levosimendan exerts its positive inotropic action by direct binding to troponin C, enhancing its affinity for calcium in a calcium-dependent manner [3,4]. Thus, the gradual decline in intracellular calcium concentration during the course of diastole decreases the drug's calcium sensitizing effect, thereby preventing a postulated adverse influence on myocardial relaxation.

In animal studies, levosimendan seemed to improve left ventricular (LV) diastolic function by increasing the rate of relaxation and thus reducing relaxation time and by improving diastolic filling. Indeed, besides inotropy, levosimendan had a positive lusitropic effect on myocyte strips from human failing hearts, as it reduced relaxation time [5]. Pagel et al. showed that levosimendan had no deleterious effect on myocardial relaxation in normal dogs while it improved diastolic function in dogs with heart failure [6]. In another study in conscious dogs with experimental HF, the drug reduced the time constant of isovolumic relaxation (Tau, i.e., the exponential decay of LV pressure during isovolumic relaxation) and increased the peak rate of mitral flow (dV/dtmax). Those effects persisted in exercise, during which the drug prevented the increase in mean left atrial pressure and end-diastolic pressure [7]. Besides the mechanism of calcium-dependent troponin C binding, the positive lusitropic effect of levosimendan may also be mediated in part through cyclic adenosine monophosphate (cAMP) or ATP-sensitive potassium channel activation [8,9].

In the clinical setting, intracoronary infusion of levosimendan in patients with dilated cardiomyopathy increased dP/dtmax and reduced Tau, as documented by a micromanometer-tipped catheter placed in the left ventricle, over a range of different heart rates, hence exerting both an inotropic and a lusitropic effect, respectively, without however affecting the force-frequency or the relaxation-frequency relationship [10]. In a small randomized study in patients with advanced HF, levosimendan improved transmitral flow patterns and mitral annulus diastolic velocities in addition to reducing neurohormonal activation and pro-inflammatory cytokines [11]. Levosimendan has also been shown to have a positive effect on diastolic function in other settings including cardiac surgery [12,13] and post-ischemic stunning [14]. However, the effects of the drug on diastolic function may be difficult to interpret, as diastolic function may also be improved by the reduction in LV afterload and preload resulting from its vasodilatory effect, while changes in left atrial pressure and the positive chronotropic effect of levosimendan may further affect LV diastolic indices.

2.2. Remodeling

Levosimendan has been shown to attenuate cardiac remodeling in different animal experimental settings. In a model of hypertension-induced myocardial hypertrophy in salt-sensitive Dahl/Rapp rats on a high-salt diet, the active metabolite of the drug, OR-1896, prevented hypertrophy when given orally for 7 weeks, without affecting blood

pressure [15,16]. In addition, the drug improved cardiac function, attenuated the increase in natriuretic peptides and reduced animal mortality. The above beneficial effects were associated with reduction in cardiomyocyte apoptosis, attenuation of myocardial calcium-handling protein disturbances (decrease in SERCA2, and SERCA2a/Na-Ca exchanger ratio) and reduction in myocardial senescence, as determined by cardiac p16 mRNA expression. In another model of post-infarct cardiac remodeling in diabetic Goto-Kakizaki rats, oral levosimendan, given for up to 12 weeks post myocardial infarction, reduced myocardial remodeling [17–19]. At the same time, the drug improved cardiac function, reduced heart failure, attenuated cardiomyocyte apoptosis, reduced levels of myocardial IL-6, monocyte chemo-attractant protein-1 and connective tissue growth factor and myocardial senescence and prevented disturbances in myocardial calcium-handling protein expression. In addition, it also modulated (up- or down-regulated) the expression of several genes, including those involved in the renin-angiotensin-aldosterone system and in glycerol-lipid metabolism.

A favorable modulation of extracellular matrix metabolism by levosimendan may partly explain the prevention of cardiac remodeling. More specifically, levosimendan prevented *in vitro* the migration of adult rat cardiac fibroblasts induced by IL-1 β , a key process in cardiac remodeling, by inhibiting the secretion of matrix metalloproteinase (MMP)-9 [20]. In addition, in the clinical setting, levosimendan reduced the circulating levels of MMP-2 in patients with acutely decompensated heart failure [21,22].

2.3. Endothelial function

In animal studies, levosimendan induced an increase in coronary blood flow in anesthetized pigs by enhancing nitric oxide (NO) production [23]. This effect was mediated by an increase in the expression of endothelial NO synthase (eNOS) through activation of extracellular-signal-regulated kinases (ERK), protein kinase B (Akt/PKB) and p38 mitogen-activated protein kinases (MAPK), while activation of mitochondrial ATP-sensitive potassium channel was also involved. In a small randomized clinical study in hospitalized HF patients levosimendan improved endothelial function when compared to placebo *in vivo*, as documented by an increase in endothelium-dependent flow-mediated dilatation of brachial artery. This effect was associated with a reduction in plasma levels of soluble intercellular adhesion molecule-1 (sICAM-1) and soluble vascular cell adhesion molecule-1 (sVCAM-1) [24].

2.4. Ventriculo-arterial coupling

Ventriculo-arterial coupling describes the relationship between myocardial contractility and arterial afterload and thus represents a measure of the efficiency of the cardiovascular system. Ventriculo-arterial coupling is determined by the ratio of end-systolic elastance (Ees, i.e., the slope of end-systolic pressure-volume relationship) to effective arterial elastance (Ea, i.e., the ratio of end-systolic arterial pressure to stroke volume). In anesthetized dogs, levosimendan increased LV Ees/Ea ratio, which is consistent with an improvement in LV-arterial coupling, as a result of an increase in LV contractility (and thus in Ees) and a reduction in LV afterload (and thus in Ea) [25]. The same effect was also observed in pulmonary circulation. In an experimental model of acute right ventricular (RV) dysfunction in pigs, induced by repetitive episodes of RV ischemia/reperfusion in the presence of temporary pulmonary artery constriction, levosimendan restored RV-arterial coupling to normal levels, as it increased RV contractility and reduced RV afterload [26].

In the clinical setting, in patients with ischemic LV dysfunction undergoing elective coronary artery bypass grafting surgery, levosimendan administered after induction of anesthesia and before the operation, both increased LV contractility and reduced LV afterload and thus improved LV-arterial coupling [27].

2.5. Ischemia-reperfusion, stunning and coronary circulation

Levosimendan may protect the myocardium against ischemia and reperfusion injury. The drug bears ischemic conditioning properties, as it activates mitochondrial ATP sensitive potassium channels that hold a key role in myocardial protection [28]. Animal studies in pigs, rabbits and rats have shown that levosimendan administration before index ischemia or during reperfusion limited infarct size, an effect consistent with pre- and post-conditioning [29–32]. Besides infarct size limitation, the drug also had a favorable effect on the incidence of arrhythmias, myocardial functional recovery and myocardial metabolism during reperfusion [30–33]. In addition to mitochondrial ATP-sensitive potassium channel activation, modulation of NO synthesis and involvement of the phosphatidylinositol 3-kinase (PI3K) pathway also seem to play a role in pharmacologic conditioning afforded by levosimendan [30,31]. The conditioning effects of the drug may have implications for acute coronary syndromes undergoing reperfusion and for elective cardiac surgery [29]. Indeed, in a small randomized study in patients undergoing elective coronary artery bypass surgery, pretreatment with levosimendan reduced post-operative troponin elevation [34].

Levosimendan has also been shown to improve systolic and diastolic function of stunned myocardium in the context of acute coronary syndromes (ACS). More specifically, in ACS patients who underwent coronary angioplasty, the drug caused an upward and leftward shift of the pressure-volume loops, consistent with enhancement of contractility [14]. In addition, levosimendan also improved echocardiographic indices of LV diastolic function after primary angioplasty in a randomized study of patients with anterior myocardial infarction [35].

Finally, besides the ischemic conditioning and anti-stunning effects, levosimendan also increased coronary blood flow in anesthetized pigs by enhancing NO release, as stressed earlier [23]. The drug has further been shown to attenuate vasospasm induced by norepinephrine or 5-hydroxytryptamine in isolated grafts from internal mammary and radial arteries, along with an anti-aggregation effect on platelets *in vitro* [36,37], an effect that may also have implications in coronary artery bypass grafting surgery.

2.6. Inflammation

Levosimendan has been shown to exert anti-inflammatory effects *in vitro*. More specifically, the drug attenuated the expression of pro-inflammatory cytokines interleukin (IL)-6 and IL-8 induced by IL-1 β in isolated human myocardial cells as well as the expression of adhesion molecules E-selectin and ICAM-1 and the adhesion of polymorphonuclear neutrophils to isolated human endothelial cells [38]. Those effects were partly mediated by the activation of mitochondrial ATP-dependent potassium channels. In addition, the drug inhibited the production of reactive oxygen species in isolated human polymorphonuclear neutrophils [39].

Clinical studies have shown that levosimendan bears anti-inflammatory effects in HF patients. In a series of small randomized trials in patients hospitalized with acutely decompensated HF, levosimendan reduced the plasma levels of high-sensitivity C-reactive protein, IL-6, tumor necrosis factor (TNF)- α , TNF- α receptor and soluble Fas and attenuated the increase of circulating markers of oxidative and nitrosative stress (protein carbonyls, malondialdehyde and nitrotyrosine) observed in the placebo group while improving cardiac function and reducing natriuretic peptides [40–43]. Some of those anti-inflammatory effects were sustained for up to 30 days after a single 24-hour infusion [43]. The anti-inflammatory effects of levosimendan, besides reflecting the improvement in cardiac function and central hemodynamics in the context of decompensated HF, are *per se* important and may have further implications in other conditions besides HF, such as sepsis and septic shock, as described in detail later.

3. Levosimendan beyond the heart: effects on peripheral organs

3.1. Kidneys

In preclinical studies *in vivo*, levosimendan has been shown to protect the kidneys from ischemia and reperfusion injury induced by renal artery clamping in anesthetized pigs and in rabbits by preventing oxidative stress and apoptosis [44,45]. These beneficial effects were shown to be dependent on mitochondrial ATP-sensitive potassium channel opening and NO synthase activation [44]. The renal anti-oxidative properties of levosimendan have also been documented in male Wistar-albino rats [46]. Furthermore, the drug has been shown to protect mice from experimental renal dysfunction caused by endotoxemia [47]; levosimendan prevented lipopolysaccharide (LPS)-induced acute renal failure, without abrogating LPS-induced inflammatory response, an effect that resulted possibly from its vasoactive properties. In addition, the drug blocked angiotensin II-mediated mesangial cell contraction in the context of endotoxemia, which in turn may theoretically increase glomerular filtration area and thus glomerular filtration rate (GFR) [47].

In clinical studies, levosimendan has been shown to protect renal function after cardiac surgery as well as in the context of acute HF [48]. In a small randomized study in 30 sedated and mechanically ventilated patients having undergone uncomplicated cardiac surgery with cardiopulmonary bypass and with normal renal function assessed by renal vein thermodilution, levosimendan increased cardiac index, renal blood flow and GFR and reduced renal vascular resistance, without affecting renal oxygen consumption or renal oxygen extraction compared to placebo [49]. Therefore, the renal effects of levosimendan can be attributable to the increase in cardiac output in combination with afferent arteriole vasodilatation. In contrast, dopamine causes vasodilatation both on the afferent and the efferent arteriole of the glomerulus, thus increasing profoundly renal blood flow without having a notable effect on GFR. In a larger randomized trial in 128 patients with impaired LV function who underwent mitral valve surgery, levosimendan, given after the removal of the aortic clamp on top of standard inotropic therapy, prevented renal function worsening during the first postoperative days compared to placebo [50]. In another small randomized trial in 21 patients with acute HF and moderate renal impairment, levosimendan improved central hemodynamics (cardiac index, pulmonary capillary wedge pressure) and increased renal blood flow as evaluated by renal artery Doppler, increased GFR and urine output compared to placebo over 3 days [51]. The drug also prevented renal function worsening during the first week after cardiac transplantation compared to standard inotropic therapy in a randomized study in 94 patients [52]. The reno-protective effects of levosimendan have further been confirmed by three meta-analyses, two concerning cardiac surgery patients and one a mixed population. Levosimendan reduced the risk of acute kidney injury and the risk of dialysis and in one of the meta-analyses also reduced mortality [53–55].

In acute HF, levosimendan has been shown to be more effective than dobutamine in improving GFR over a period of up to 72 h in a randomized study in 88 patients [56]. Particularly in patients with acute HF and renal function impairment, a frequent comorbidity in those patients, a 24-hour levosimendan infusion but not placebo increased GFR for up to 14 days after infusion, as shown by a randomized study in 66 patients [57]. In an observational study in 96 patients with acute HF and impaired GFR, levosimendan reduced the incidence of in-hospital renal function worsening and the levels of cystatin C [58]. The renoprotective effect of levosimendan in the context of acute HF seems to be mediated through an increase in renal blood flow by renal artery vasodilatation, as documented by intravascular renal artery Doppler [51]. Levosimendan also improved renal function in advanced HF patients awaiting cardiac transplantation, as shown by a randomized trial in 40 patients [59]. Three ongoing randomized trials in severe HF with impaired renal function (ELDORADO, NCT02133105), in adult cardiac surgery patients

(LEVOAKI, NCT02531724) and in pediatric cardiac surgery patients (MiLe-1, NCT02232399), are expected to shed some new light on the renal effects of levosimendan.

3.2. Liver

Levosimendan has protective effects during hepatic ischemia and reperfusion injury as demonstrated both *in vitro*, in isolated rat hepatocytes, and *in vivo* [60–62]. More specifically, the drug protected the hepatocytes from oxidative and apoptotic changes after ischemia-reperfusion through mechanisms dependent upon the modulation of NO release by eNOS and inducible NOS (iNOS), the activation of mitochondrial ATP-dependent potassium channels and the activation of cyclooxygenase (COX)-1 [60,61,63]. Such findings may have important implications for liver surgery, particularly hepatic transplantation.

Experimental and clinical evidence suggests that levosimendan may act as a selective hepatic vasodilator, as it was able to improve hepatic perfusion through both the hepatic artery and the portal vein. Levosimendan increased blood flow and reduced vascular resistance in liver as documented by the radioactive microsphere technique in anesthetized dogs [64]. The drug also improved hepatic microcirculation and portal blood flow as measured by laser Doppler flowmeter and ultrasound flowmeter probes in rats model of hepatic ischemia [60,62]. Similar effects on portal circulation were found in experimental sepsis in pigs, where the vascular response to levosimendan was not accompanied by any changes in systemic blood pressure [65]. Similarly, in patients with low cardiac output following cardiac surgery, levosimendan both increased portal vein blood flow and reduced hepatic artery resistance [66]. Finally, in septic shock patients, levosimendan increased hepatic perfusion, as documented non-invasively by indocyanine green plasma disappearance rate (ICG-PDR) [67].

3.3. Gut and splanchnic vasculature

In addition to the beneficial effects on hepatic blood flow, levosimendan has been shown to improve blood flow and reduced vascular resistance in the small intestine in anesthetized dogs and increase gastric mucosal oxygenation in anesthetized dogs [64,68]. The drug also improved intestinal blood flow and intestinal mucosal oxygenation in experimental sepsis both in pigs and in sheep [65,69], although this latter effect was questioned by another study in pigs with endotoxemic shock, in which levosimendan did not increase hepatosplanchnic perfusion [70].

In the clinical setting, in patients undergoing abdominal aortic surgery, levosimendan improved gastric mucosal oxygenation, as documented by gastric mucosal-arterial pCO₂ gradient, but it did not increase total splanchnic blood flow, as estimated by ICG-PDR [71].

3.4. Lungs and respiratory muscles

Levosimendan has further been shown to affect lungs and pulmonary function. In animal studies, the drug protected the lungs in rats against direct ischemia and reperfusion injury accomplished by unilateral hilar occlusion but also against acute lung injury in the context of sepsis, myocardial ischemia or limb ischemia [72–77]. Besides its well known anti-ischemic, anti-apoptotic and anti-inflammatory properties that seem to be effective also in lungs, the drug further causes vasorelaxation in pulmonary circulation through activation of ATP-sensitive potassium channels and activation of cAMP and cGMP pathways [78]. Since this effect concerns both pulmonary arteries and pulmonary veins, levosimendan could be supposed to cause a reduction of both RV afterload and pulmonary hydrostatic pressures. As a result, in a pilot randomized clinical study, levosimendan improved RV function through pulmonary vasodilatation in septic patients with acute respiratory distress syndrome (ARDS) [79].

Respiratory muscle weakness may develop in the course of several conditions including heart failure, chronic obstructive pulmonary

disease (COPD) and in ventilated critically ill patients [80]. Among other factors, reduced calcium sensitivity of contractile proteins plays an important role in respiratory muscle dysfunction in these conditions [80]. Levosimendan has been shown to enhance *in vitro* the contractility of isolated diaphragm muscle fibers from healthy subjects and COPD patients as well as from rats with heart failure by improving calcium sensitivity, acting mainly on slow fibers and less on fast fibers [81]. *In vivo*, the drug attenuated oxidative tissue damage in diaphragm of mechanically ventilated mice with septic shock [82]. In a small randomized placebo controlled trial, levosimendan has been shown to improve contractile efficiency of the diaphragm in healthy subjects and reverse the development of fatigue after inspiratory muscle loading [83].

3.5. Central nervous system

Levosimendan is known to cross the blood–brain barrier and may act beneficially in the central nervous system (CNS) by causing arterial vasodilation and/or neuro-protection. Indeed, there is very limited experimental and clinical evidence suggesting a potential neuro-protective role of the drug against brain and spinal cord ischemia and reperfusion injury, as well as against brain damage in the context of subarachnoid hemorrhage (SAH).

Levosimendan has been shown to protect the brain *in vitro* from mechanical trauma in isolated hippocampus slices from mice [84]. In *in vivo* animal studies of CNS ischemia and reperfusion, levosimendan increased blood flow, limited brain infarct size and edema and attenuated local TNF- α and ICAM-1 expression in male Wistar rats subjected to 60-min middle cerebral artery occlusion, without affecting neurological outcome or mortality [85]. In addition, it also protected spinal cord from neurological, histopathological and biochemical changes in New Zealand rabbits subjected to 30-min abdominal aorta clamping [86]. However, in another *in vivo* study, the drug had no effect on cerebral perfusion or edema or local expression of pro-inflammatory cytokines in male Wistar rats subjected to ischemia by 15-min carotid artery clamping combined with hypoxia by ventilation with 6% oxygen [87].

In human studies, a 48-hour levosimendan infusion increased cerebral intravascular oxygenation, as evaluated by near-infrared spectroscopy, in 16 critically ill infants suffering from low cardiac output syndrome due to congenital cardiac defects, without a simultaneous change in cerebral blood volume [88]. The amelioration of cerebral oxygenation in the absence of change in cerebral blood volume could be attributed to the decreased blood transit time due to the global circulatory improvement rather than to cerebral vasodilation *per se*. In another small study, however, oral levosimendan, given in 5 escalating doses at 18-day intervals per each dose, increased cerebral blood flow in 16 patients with ischemic stroke or transient ischemic attack, as documented by transcranial Doppler assessment of middle cerebral artery flow velocities [89].

Subarachnoid hemorrhage may result in detrimental neurological effects through sympathetic overstimulation, oxidative stress, inflammatory activation and myocardial stunning that may lead, in turn, to decreased cerebral perfusion, cerebral vasospasm, dysfunction of blood-brain barrier, edema and finally brain injury [90]. Levosimendan may protect the brain from those effects by its vasodilatory, anti-inflammatory and cardiac enhancing properties. Indeed, in an experimental SAH model in rabbits, levosimendan prevented cerebral vasospasm [91], while a case report in a patient with SAH documented improved neurologic outcomes [92].

4. Levosimendan beyond acute heart failure: effects on other cardiovascular and non-cardiovascular conditions

4.1. Advanced HF

Patients with advanced heart failure suffer from marked limitation of exercise capacity, severe symptoms, often unresponsive to drug therapy, lack of tolerance to disease-modifying therapies, progressive

deterioration of multiple organ function and frequent hospital admissions [93]. These patients are often dependent on continuous inotropic support for severe symptoms. In this setting, repetitive or pulsed levosimendan infusions, that take advantage of the long-lasting metabolite OR-1896, represent an attractive alternative. Several clinical studies have provided encouraging evidence on this approach in terms of functional status, hemodynamics, neurohormonal and inflammatory markers, quality of life and clinical outcomes [41,94–102]. A recently published meta-analysis of 7 randomized trials on 438 patients showed a significant reduction in mortality after an average follow-up of 8 months [odds ratio (OR) versus placebo, 0.54 (0.32–0.91), $p = 0.02$] [103,104]. However, the recently published multicenter randomized trial LevoRep failed to meet its primary endpoint of improvement in functional capacity and quality of life, as assessed by 6-min walked distance and Kansas City Cardiomyopathy Questionnaire, although it documented a reduction in mortality, acute heart failure episodes and heart transplantation [105]. The available evidence on the intermittent use of levosimendan in advanced HF is reviewed in detail in an expert consensus document [106].

4.2. Sepsis and septic shock

Levosimendan has been shown to improve multiple aspects of organ dysfunction in animal models of sepsis. In long series of studies in animals including rabbits, pigs, rats and sheep with experimental sepsis, levosimendan improved cardiac systolic and diastolic function, central haemodynamics, as well as liver, kidney and pulmonary function and enhanced hepatic and splanchnic perfusion, prevented pulmonary vasoconstriction and acute lung injury [65,73,74,82,107–110]. In terms of underlying mechanisms, levosimendan exerted anti-inflammatory effects both *in vivo* and *in vitro* and decreased iNOS expression and activity and NF-kappaB-dependent transcription *in vitro* [107,109,111,112].

In the clinical setting, according to a meta-analysis of 7 studies on 246 patients with severe sepsis or septic shock, levosimendan significantly reduced mortality compared to standard inotropic therapy (risk ratio, 0.79 (0.63–0.98), $p = 0.03$), while it was also followed by higher cardiac index and lower lactate concentration, despite similar blood pressure levels and norepinephrine use [113]. Additional studies have provided more insights into the potential mechanisms underlying this apparent beneficial effect in septic patients. These studies have documented improvement in cardiac performance, central hemodynamics and peripheral organ perfusion, including renal, hepatic and gastrointestinal perfusion, enhancement of renal and hepatic function, improvement of right ventricular performance in ARDS, resuscitation of microcirculation and enhancement of mitochondrial function with anti-oxidative properties [48,67,79,114–116]. The ongoing Levosimendan for the Prevention of Acute Organ Dysfunction in Sepsis (LeoPARDS) study will provide further evidence on the efficacy of levosimendan in improving organ dysfunction and the underlying mechanisms in patients with septic shock and evaluate its biological mechanisms of action [117].

4.3. Perioperative prophylaxis

The aforementioned protective effects of levosimendan against ischemia and reperfusion injury in multiple organs including the heart, kidneys, liver, lungs, brain and spinal cord as well as its vasodilating effects on several vascular beds such as the coronary, pulmonary circulation and splanchnic circulation may render the drug useful for the peri-operative protection of patients undergoing cardiac or non-cardiac surgery. Indeed, several studies have provided encouraging evidence on favorable effect of the drug when given peri-operative in patients undergoing different types of cardiac surgery including coronary artery bypass grafting, aortic valve replacement or correction of congenital defects, particularly in patients with poor cardiac function [12,13,34,118–124]. The available evidence on the perioperative

use of levosimendan in cardiac surgery has recently been compiled by a European expert panel [125]. The potential role of levosimendan in optimizing cardiac performance in HF patients undergoing major non-cardiac surgery has also been stressed [126]. The ongoing CHEETAH trial (NCT00994825) of levosimendan infusion in patients who develop low cardiac output syndrome after cardiac surgery is designed to enroll 1000 patients and is expected to provide important insights into the management of patients undergoing cardiac surgery.

4.4. Weaning

Given its potential beneficial effects on respiratory function, levosimendan may potentially facilitate weaning from mechanical ventilation. In addition, it also seems to improve splanchnic mucosal oxygenation that is depressed by mechanical ventilation [127], while the effects of the drug on respiratory function in patients with difficult weaning from mechanical ventilation are being investigated (NCT01721434). It has further been suggested that levosimendan may be used for the weaning of patients from mechanical circulatory support or treatment with other inotropes or vasoconstrictors [128–130], while it has been shown effective in facilitating weaning from cardiopulmonary bypass in patients with LV dysfunction after coronary artery bypass surgery [131].

4.5. Subarachnoid hemorrhage

Subarachnoid hemorrhage, besides its detrimental neurologic effects, may also cause myocardial stunning through sympathetic over-activation that may in turn lead to stress cardiomyopathy or cardiogenic shock [90]. Besides its potentially neuro-protective role, levosimendan may also improve cardiac function in neurologically stunned myocardium in the context of SAH, as suggested by reports of 4 cases in total treated with levosimendan for either cardiogenic shock or stress cardiomyopathy associated with SAH [92,132,133].

5. Summary and call for action

Levosimendan is currently approved in many countries worldwide for acutely decompensated heart failure with low cardiac output. Based on the compiled evidence described in detail above, besides the typical scenario of low cardiac output, the drug is expected to have favorable effects in other conditions associated with acutely decompensated heart failure, including acute coronary syndromes, RV failure, subarachnoid hemorrhage and cardiac surgery, either with preserved organ function or complicated by renal dysfunction, hepatic injury or cardiogenic shock with multi-organ dysfunction. The above clinical scenarios are outlined in Fig. 2.

Bearing in mind the accumulated evidence, levosimendan may have favorable effects in several conditions beyond the heart and acute heart failure. It can confer protection of renal, hepatic, brain and spinal cord function in cases with ischemia and reperfusion injury. Moreover, levosimendan can be effective during brain injury or cardiac stunning caused by subarachnoid hemorrhage, respiratory dysfunction, sepsis and septic shock, peri-operative events, advanced heart failure as well as during weaning from mechanical ventilation, inotropes or mechanical circulatory support (Fig. 3). All the aforementioned clinical conditions outlined in Figs. 2 and 3 represent potential challenging fields of clinical research. At least preclinical data are available for all of those fields, while clinical evidence has also been accumulated for some of them, thus providing the grounds for further clinical testing. In addition, further research fields are emerging. Preclinical evaluation of the cardioprotective effects of levosimendan against doxorubicin-induced toxicity is in progress and the first results are expected shortly [Personal communication]. A call for action for further research on the effects of levosimendan beyond inotropy, the heart and acute heart failure is

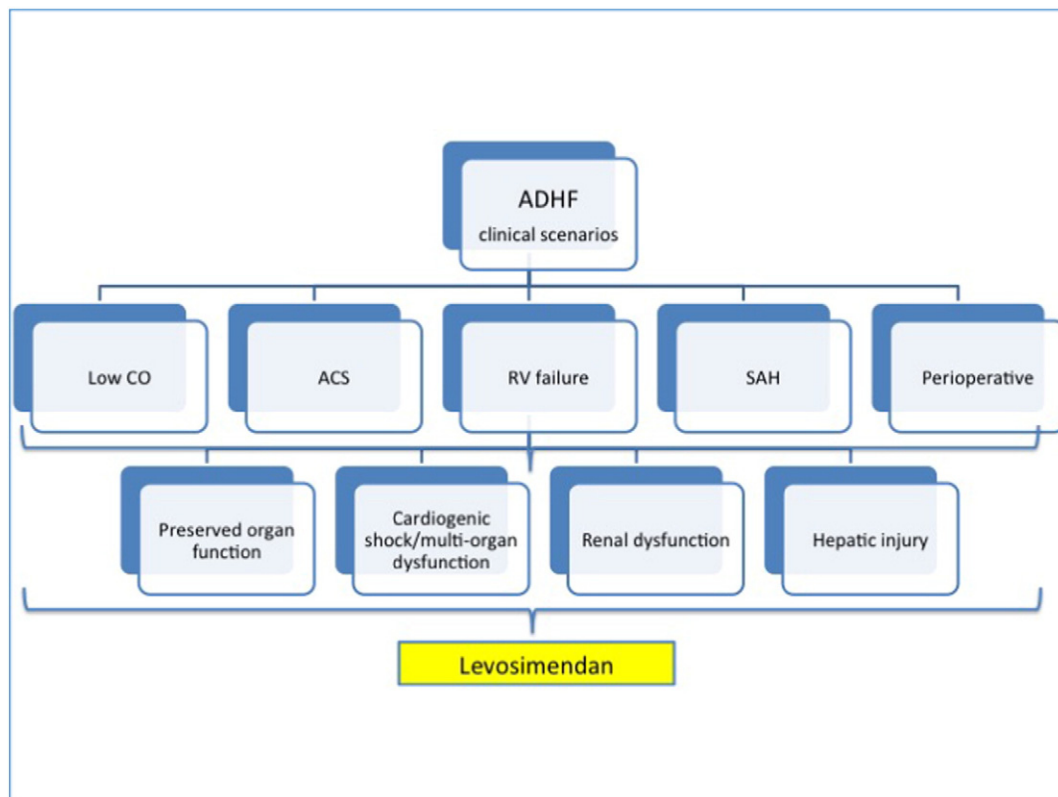


Fig. 2. Clinical scenarios in the context of acutely decompensated heart failure, in which levosimendan may play a beneficial role.

framed in Table 1. Additional preclinical studies in fields with limited evidence, early-phase proof-of-concept clinical trials in fields where there is sufficient preclinical evidence and more advanced-phase

clinical trials in fields with sufficient early-phase clinical evidence constitute the required next steps to advance our knowledge and explore potential novel indications of levosimendan.

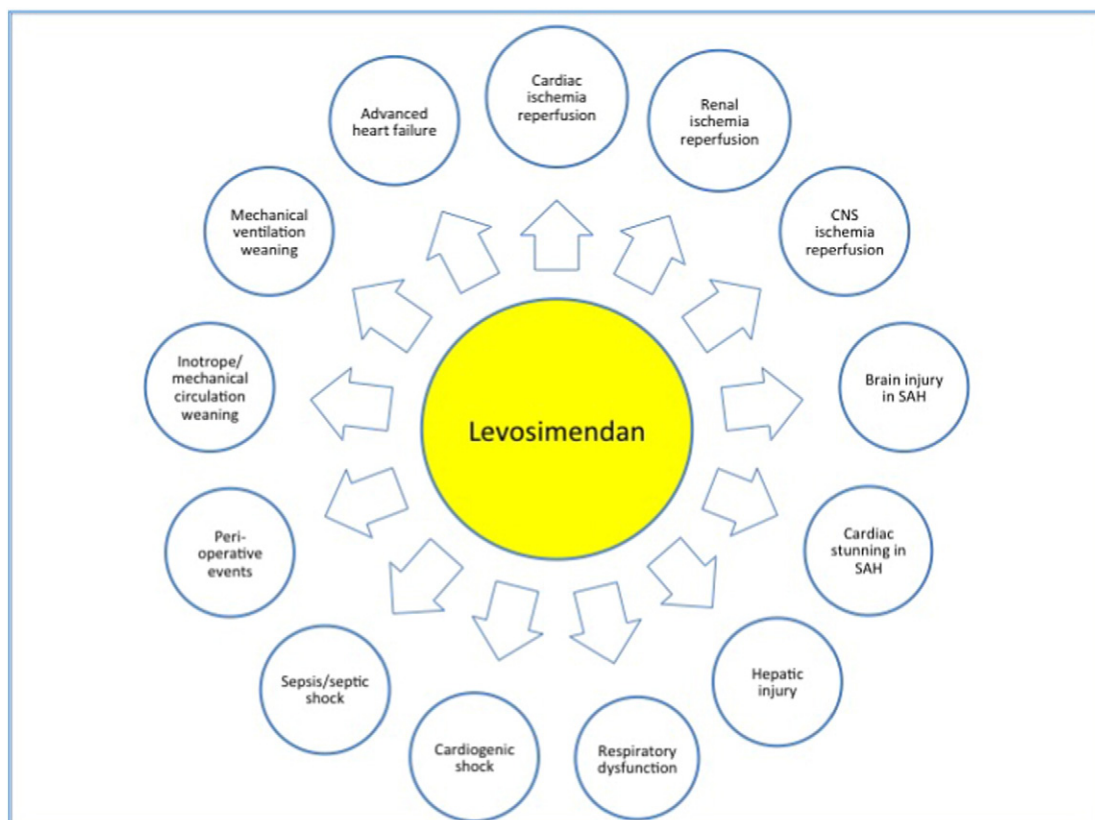


Fig. 3. Summary of the favorable effects of levosimendan beyond inotropy, the heart and acute heart failure.

Table 1

Call for action for further research on the effects of levosimendan beyond inotropy, the heart and acute heart failure.

Field of interest	Level of evidence	Suggested action
<ul style="list-style-type: none"> Cardiac remodeling CNS protection Subarachnoid hemorrhage Cardio-Oncology Hepatic function Gut and splanchnic circulation 	Limited preclinical data	Further preclinical research
<ul style="list-style-type: none"> Relaxation and diastole Inflammation Myocardial ischemia/-reperfusion Endothelial function Ventriculo-arterial coupling Pulmonary function Weaning Advanced HF (pulsed infusions) Ongoing RCTs Peri-operative prophylaxis Renal function Sepsis 	Sufficient preclinical and/or early-phase clinical data	Proof-of-concept or early-phase clinical trials Advanced-phase clinical trials

CNS: central nervous system; RCTs: randomized clinical trials; HF: heart failure.

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